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Two novel synthetic peptoids exhibit rapid *in vitro* killing of methicillin-resistant *Staphylococcus pseudintermedius*

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Introduction

• Methicillin-resistant *S. pseudintermedius* (MRSP) are of increasing concern due to its recent spread amongst dog populations worldwide (Perreten et al., 2010).

• Limited treatment options are available for MRSP, thus alternative treatment is required to combat these multidrug-resistant microorganisms in the future.

• Peptoids are oligomers of N-substituted glycines and may mimic biologically active peptides by showing antimicrobial properties.

• Peptoids resemble peptides except that the side chains are appended to the nitrogen atom of the backbone rather than to the α-carbons. They are also characterised by being more stable *in vitro* towards heat, salt, pH fluctuations and organic solvents compared to peptides. *in vivo*, peptoids are stable to proteolysis whereas peptides are rapidly degraded.

Objective

• To assess the *in vitro* efficacy of two newly developed peptoids against MRSP and methicillin-susceptible *S. pseudintermedius* isolates of canine origin

Materials and Methods

• Prior to the study, 10 newly developed peptoids were tested for their *in vitro* efficacy and hemolysis against various bacterial species. A lysine peptoid hybrid (B1) and a pure peptoid (D2) showing both a low minimum inhibitory concentration (MIC) and a low rate of hemolysis against *S. pseudintermedius* were selected for this study.

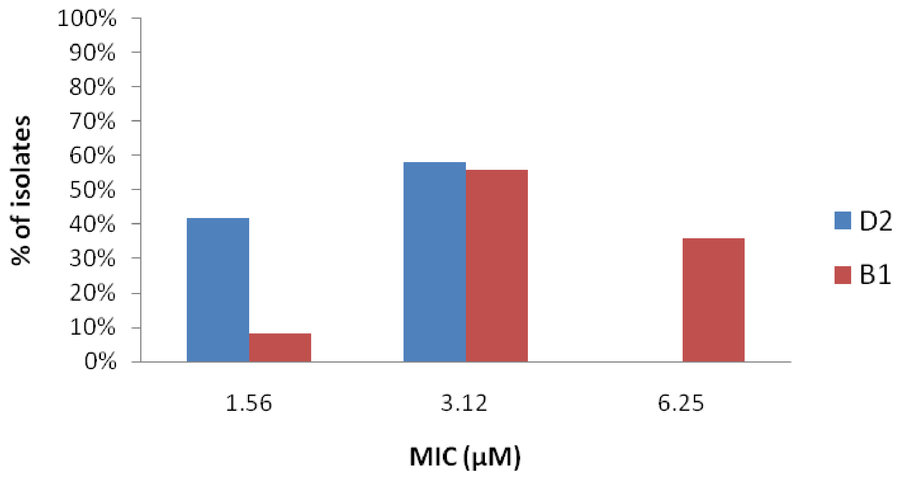
• B1 and D2 were tested for their *in vitro* activity against 50 clinical *S. pseudintermedius* isolates of canine origin using the broth microdilution method (CLSI, 2008). Ten of these isolates were MRSP and 40 isolates were MSSP, and all isolates had been collected at our diagnostic lab between 2007 and 2010.

• B1 and B2 were also tested in a time kill kinetic study against one representative *S. pseudintermedius* isolate. Survival of a standard inoculum ($5*10^5$) of this isolate was observed over time after inoculation without peptoid, at 1*MIC and at 4*MIC.

Results

MIC determinations (Fig .1)
• Low MIC's ranging from 1.56-6.25 µM were observed for B1 and D2. MICs did not differ between MSSP and MRSP.
• MICs were normally distributed → no obvious evidence of resistance in the 50 isolates tested.

Fig 1. MIC distributions



Time kill kinetics (Fig 2a and 2b)
• Both B1 and D2 had a concentration-dependant antimicrobial effect on *S. pseudintermedius*.
• B1 acted more rapidly with complete killing at 4 * MIC in 30 min.
• D2 was slightly slower taking 2 hours to kill at 4 * MIC.

Fig 2a. Time kill curves - B1

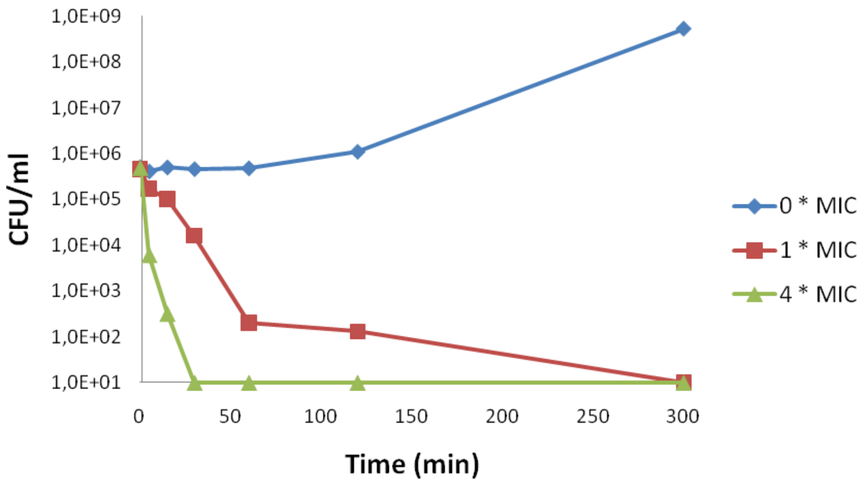
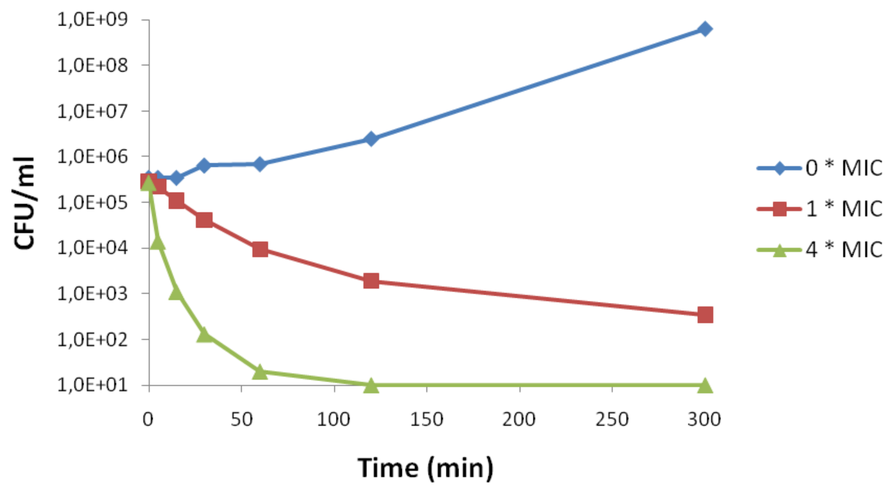


Fig 2b. Time kill curves - D2



Conclusions

• Two novel peptoid compounds were shown to have a rapid concentration-dependant effect against *S. pseudintermedius* of canine origin, irrespective of antibiotic resistance phenotypes.

• The rapid killing resembles the pharmacodynamics of antiseptics but the mechanism of action is unknown.

• The next step will be to test the effect and toxicity of topical formulations of the two compounds *in vivo*, for example in a mice skin infection model.

References

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